

REMARKS

No amendments have been made by the present communication. Claims 1-38, 49-51 and 53-58 are pending in this application. Applicant respectfully requests reconsideration of the present application in view of the reasons that follow.

I. Rejections under 35 USC § 112, 1st Paragraph

Claims 1-38 and 53-58 stand rejected under 35 USC § 112, 1st paragraph as allegedly failing to comply with the written description requirement. In particular, the Office asserts that "the specification does not provide adequate written description of the claimed 'amount' of the disclosed compound 'to provide' the claimed C_{max} range, AUC range, or amount of compound in the subject's blood or plasma 24 hours after administration, and purported to have anticancer activity." Office Action, dated 12/4/2009, p. 4. Applicant respectfully traverses this rejection.

To satisfy the written description requirement a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., *Moba, B.V. v. Diamond Automation, Inc.*, 325 F. 3d 1306, 1319, (Fed. Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F. 2d 1555, 1563 (Fed. Cir. 1991). An Applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F. 3d 1565, 1572 (Fed. Cir. 1997). More specifically, the written description requirement for a genus may be satisfied by the disclosure of a representative number of species by actual reduction to practice or by reduction to drawings. *Id.* It therefore is not necessary to describe each species of a genus to provide written description for the genus. An analysis of compliance with the written description requirement is conducted from the standpoint of one of skill in the art at the time the application was filed. See, e.g., *Wang Labs. V. Toshiba Corp.*, 993 F.2d 858, 865 (Fed. Cir. 1993). The present application meets these standards.

First, the present application provides considerably more information regarding how to achieve the plasma/blood levels recited in the claims than discussed in the Office Action. While the discussion in the Office Action focuses on the oral dosage amounts of the recited compound in the working examples, it fails to acknowledge the results of those dosages. As shown in Table 5 of the application, the various dosages achieve a range of C_{\max} in plasma from 48 ng/mL at 3 mg/kg/day up to 3450 ng/mL at 300 mg/kg/day. Similarly, the various dosages achieve a range of AUC from 420 ng*hr/mL to 61,300 ng*hr/mL and a range of 11.1 ng/mL to 2980 ng/mL of compound in a subject's plasma 24 hours after administration. These results are directly compared in the table below and closely track the claimed ranges. Applicant submits that these results demonstrate that the indicated dosages are representative of and in fact readily achieve the full scope of the blood levels recited in the claims.

<u>Parameter</u>	<u>Range in Claims</u>	<u>Range in Working Examples</u>
C_{\max}	20 – 4,000 ng/mL	48 – 3,450 ng/mL
AUC	500 – 60,000 ng*hr/mL	420 – 61,300 ng*hr/mL
Conc. after 24 h	10 – 2,000 ng/mL	11.1 – 2,980 ng/mL

Moreover, the application discloses a wealth of other information useful to those skilled in the art in adapting dosages and dosing schedules for any particular subject. Thus, Example 4 shows that the exemplified dosages demonstrate *in vivo* anticancer activity (Table 4) and correlates plasma concentrations with tissue concentrations (Table 6). Example 5 shows that different dosing schedules also demonstrate *in vivo* anticancer activity (Table 7) and allow for the minimization of potential clinical toxicity as measured by weight loss. Example 8 demonstrates that the exemplified dosages provide significant *in vivo* inhibition of angiogenesis with low toxicity. Example 11 tracked the distribution of the compound in numerous tissues of the body, including blood. Further guidance is given for specific types of administration procedures and amounts of compound at paragraphs 14-17, 19, and 21.

In view of such guidance, the skilled artisan will readily be able to interpolate dosages between or around those demonstrated. They will be able to adjust to different routes of administration and different dosing schedules. Such adjustments would not be hit or miss in view of the basic pharmacokinetic and bioactivity evidence provided. As such, the skilled artisan will recognize that Applicant has provided sufficient representative examples of the claimed methods to show possession of the claimed invention. Withdrawal of the present ground of rejection is respectfully requested.

II. Rejections under 35 USC § 103(a)

The Office has rejected the pending claims as allegedly obvious over various combinations of Renhowe (US 6,605,617), Glade-Bender (Expert. Opin. Biol. Ther. 2003, 3:2, 263-76), and "Guidelines for the Format and Content of the Human Pharmacokinetic and Bioavailability Section of an Application" (Center for Drugs and Biologics, FDA, Department of Health and Human Services, February 1997, 1-18), hereinafter, "FDA Guidelines," alone and with other references. Specifically, claims 1-6, 9-13, 17, 19-30 35-38, 49, and 53-58 stand rejected over Renhowe, Glade-Bender and FDA Guidelines; claims 7-8 and 14-15 stand rejected over Renhowe, Glade-Bender, FDA Guidelines, and Berge (J. Pharm. Sci., 1977, 66:1, 1-19); claims 16 and 18 stand rejected over Renhowe, Glade-Bender, FDA Guidelines, and Lindell (US2003/0159702); claims 31-34 and 50-51 stand rejected over Renhowe, Glade-Bender, FDA Guidelines, and Cecil Textbook of Medicine (21st Edition, vol. 1, 2000, eds Goldman and Bennett, pp. 1060-74). Applicant respectfully traverses these rejections.

The Office notes that "the applied reference (Renhowe et al.) has a common inventor with the instant application. Based on the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e)." December 4, 2009 Office Action, p. 5. The Office further indicated that Renhowe may be disqualified as a prior art reference under 35 U.S.C. 103(c).

Applicant submits that Renhowe is disqualified as prior art under 35 USC §102(e) through the common ownership provisions of 35 USC §103(c). Under this section of the patent law, subject matter developed by another person, which qualifies as prior art only under one of more of subsections (e), (f), and (g) of 35 USC §102, shall not preclude patentability under §103 where the subject matter and the claimed invention were, at the time the claimed invention was made, owned by the same person or subject to an obligation of assignment to the same person. Applicant hereby submits the following statement of common ownership.

At the time the invention of the present application was made, both the Renhowe patent application and the present application were owned by or subject to an obligation of assignment to Chiron Corporation (n.k.a. Novartis).

Per the MPEP § 706.02(l)(2), this statement is sufficient evidence of common ownership under the statute. Therefore, as provided under 35 U.S.C. § 103(c), Renhowe cannot serve as a reference under §103(a) because the subject matter of the pending claims of the present application and the Renhowe patent were commonly owned at the time the invention was made.

Because Renhowe is not a proper reference under 35 USC §103(a) for the reasons given above, Applicant respectfully requests the withdrawal of the present rejection under 35 USC §103(a).

Even if Renhowe was a proper reference, Applicant submits that the present claims are non-obvious over Renhowe and Glade-Bender for the same reasons given in section III, below.

III. Rejections for nonstatutory obviousness-type double patenting

Claims 1-6, 9-15, 16-38 and 53-58 stand rejected for nonstatutory obviousness-type double patenting over claim 30 of US Patent No. 6,605,617 in view of Glade-Bender. Applicant respectfully traverses this ground of rejection.

It is well established that a species may be patentable over a disclosed genus to which it belongs if it meets the statutory requirements for patentability. In the context of a nonstatutory

non-obviousness rejection, the analysis parallels that for non-obviousness under 35 U.S.C. §103(a). *In re Braat*, 937 F.2d 589 (Fed. Cir. 1991).

Applicant respectfully submits that the Office has failed to establish a prima facie case of obviousness over claim 30 of Renhowe. The present claims recite methods for alleviating the symptoms of or halting the progression or worsening of the symptoms of gastrointestinal stromal cancer, glioma, melanoma, bladder cancer and renal cancer using 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one (hereinafter, "the quinolinone"). Claim 30 does not recite any of these cancers and the Glade-Bender reference does not establish that the present quinolinone will be useful to treat the recited cancers.

The Glade-Bender reference describes a number of protein and small-molecule inhibitors of VEGF (none of which include the present quinolinone) that have shown anti-cancer activity. However, article itself acknowledges unpredictability in whether any particular cancer will respond to VEGF inhibition:

...it is clear that not all experimental tumours are equivalently, or even effectively, suppressed by VEGF antagonism. It has been shown in murine xenograft models that while anti-VEGF antibody therapy almost totally suppresses Wilms' tumour growth, it only partially suppresses neuroblastoma and is ineffective against rhabdoid tumour. This is despite VEGF being expressed in all three tumour types. Therefore, it may be difficult to predict whether a particular type of tumour, let alone an individual patient's cancer, will respond to VEGF inhibition. Indeed, the correlative studies on VEGF levels from various clinical trials have been unable to reliably predict which patients will respond to VEGF blockade therapy. (*Id.*, p. 270, last full paragraph, left column.)

Furthermore, evidence in Glade-Bender that certain VEGF inhibitors have efficacy in certain cancers, is not likely to be a reliable predictor of the anti-cancer activity of any other particular VEGF inhibitor. First, the compounds cited by the Office as showing that VEGF inhibitors may treat melanoma, glioma and renal cell cancer differ significantly in structure

(indolinone pyrroles rather than benzimidazole quinolinones) from the present quinolinone. Such differences make blanket predictions of activity different. Indeed, Glade-Bender discloses that while SU5416 and SU6668 have "some receptor specificity, these molecules will generally inhibit families of receptors." (Glade-Bender, p. 268, last paragraph, left column.) SU5416, e.g., inhibits not only VEGF receptors, but c-kit and flt-3 receptors. In contrast, Renhowe discloses that compounds disclosed therein inhibit VEGFR1, VEGFR2 and bFGFR. Hence, despite common activity at the molecular level with regard to VEGFR inhibition, the compounds of Renhowe and Glade-Bender are not shown to have similar in vivo activity. Thus, there is no way for the skilled artisan to predict that the present quinolinone compound will be useful in treating the same cancers that SU5416 and SU6668 are useful in.

Moreover, the reference in Glade-Bender to treatment of renal cell cancer is speculative at best. The only sentence that Applicant was able to find relating to renal cell cancer on p. 269 actually begins on p. 268 and reads: "[a]s a single agent, exciting potential activity [of SU5416] was seen, predominantly in advanced colorectal disease, but also in mesothelioma, refractory Kaposi's sarcoma, head and neck cancers, melanoma, acute myelogenous leukaemia, and possibly, renal cell carcinoma." Hence, from this statement it is not clear whether SU5415 exhibits good activity against renal cell cancer or not.

In view of the unpredictability in the art acknowledged in the cited reference itself, and the significantly different chemical structures of the cited VEGF inhibitors compared to the present inhibitor, Applicant submits that the claimed methods of treating the recited cancers are not obvious. Applicant respectfully requests withdrawal of this rejection.

Claims 1-38, 49-51 and 53-58 stand provisionally rejected for nonstatutory obviousness-type double patenting over claims 1-17, 34, 49, 51-58, 66 and 70-71 of copending application 11/913,828. Applicant respectfully submits that the provisional rejection be held in abeyance until a notification of otherwise allowable subject matter in the present application is provided.

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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